Venlafaxine and Nortriptyline Reverse Acute Dexamethasone-Induced Depressive-Like Behaviors in Male and Female Mice

Ingrid B. M. B. de Souza, Layse R. F. Costa, Pamella R. F. Tiago, Fernanda C. Cagni, Ramon H. Lima,
Edilson D. Silva Junior, and Elaine C. Gavioli
Federal University of Rio Grande do Norte

Major depression can be triggered by stressful events that promote deregulation of the hypothalamic-pituitary-adrenal axis response and, in some circumstances, persistent elevation of circulating glucocorticoid levels. Animal models are widely used to investigate the mechanisms responsible for the etiology and treatment of major depression. However, to mimic the dysfunction of the hypothalamic-pituitary-adrenal axis in rodents, animals should be exposed to sustained physical and psychological stressful situations. These animal models of depression are labor intensive and impact individual animals differently. Aiming to add evidence for a new acute neuroendocrine model of depression, male and female mice were treated with a single administration of dexamethasone, and behavioral effects were evaluated in the presence and absence of the antidepressants nortriptyline and venlafaxine. Male and female Swiss mice were treated with dexamethasone (0.07 mg/kg, subcutaneously) and the mouse behavior was assessed in the tail suspension and open field tests at 4 h, 24 h, and 7 days after administration. Dexamethasone induced depressogenic-like states in both sexes at 4 and 24 h after injection. Additionally, acute dexamethasone increased latency to body fur licking, thus corroborating the depressive-like behavior. The treatment with nortriptyline and venlafaxine (both at 30 mg/kg, intraperitoneally) blocked dexamethasone-induced increase in the immobility time and the latency to self-care. In conclusion, the present findings suggest that a single administration of dexamethasone induces depressive-like states in male and female mice, and these behavioral alterations are counteracted by conventional antidepressants. Ultimately, these data provide new evidence for an acute neuroendocrine model of depression.

Public Health Significance
Depression causes a significant impact in the public health. Innovative treatments are needed and rodents are widely used to search for new antidepressants. However, it is labor intensive to induce a depressive state in rodents. This study provides an innovative acute way of inducing a depressive state in mice. Our findings showed that a single administration of dexamethasone promotes a depressive state in male and female mice, which is blocked by conventional antidepressants.

Keywords: dexamethasone, major depression, tail suspension test, acute exposure, splash test

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Major depression is a chronic, complex, and multifactorial psychiatric disorder associated with functional impairment, which is characterized by depressed mood and/or loss of interest in daily activities (anhedonia) and altered motivational behavior, appetite, and sleep (American Psychiatric Association, 2013). A meta-analysis study indicated that estimated 12-month prevalence for major depression is about 5% in the world population (Ferrari et al., 2013). Interestingly, epidemiological studies also reported that

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women typically have a 2-fold increased risk of major depression compared with men (Van de Velde, Bracke, & Levecque, 2010).

As is currently known, changes in monoamine neurotransmission do not entirely clarify macro- and microscopic structural alterations reported in major depression (Dean & Keshavan, 2017). Additionally, stressful life events seem to contribute to the etiology of depression. In fact, it is estimated that 85% of depressive patients experienced some stressful event prior to the onset of the disorder (Kessing, Agerbo, & Mortensen, 2003). Additionally, it is described that 40–60% of untreated patients with depression present hypercortisolism related to the activation of hypothalamic-pituitary-adrenal (HPA) axis by stressful events (Gold et al., 1986; Carroll et al., 2012).

Animal models are widely used to investigate the mechanisms responsible for the etiology and treatment of major depression as well as to check the efficacy of new antidepressant drugs. To mimic the dysfunction of the HPA axis in rodents as observed in depressive patients, animals can be exposed to physical and psychological stressful situations or exogenous administration of glucocorticoids (Sterner & Kalynchuk, 2010; Czéh, Fuchs, Wiborg, & Simon, 2016). In fact, stress-based animal models of depression (learned helplessness model, chronic mild stress, social defeat model, or chronic corticosterone injection) frequently report significant behavioral changes, such as: (a) increase in the immobility time in behavioral despair tests (i.e., forced swimming and tail suspension tests); (b) change in body weight; (c) decrease in motivational behaviors; and (iv) cognitive impairments and other physiological changes (Söderlund and Lindskog, 2018).

Ideally, an animal model should fulfill at least three major criteria: face, construct, and predictive validity. Briefly, animal models must resemble the human condition in several aspects, including (a) similarity between the behavioral phenotype and the clinical-symptom profile (face validity), (b) amelioration or attenuation by clinical effective antidepressant treatments (predictive validity), and (c) similar neurobiological basis (construct validity; Czéh et al., 2016). It is noteworthy that the most well-validated animal models of depression, including chronic mild stress, social defeat, and intracranial self-stimulation, are labor intensive, which substantially limits the rapid screening of new antidepressant drugs (Söderlund et al., 2018). By contrast, behavioral despair tests, that is, forced swimming and tail suspension tests, are used worldwide because of their ease of use, reliability across laboratories, ability to detect a broad spectrum of antidepressants, and to attend high demands of the pharmaceutical industry for screening new compounds (Czéh et al., 2016). Concerning the tail suspension test, it is based on the observation that mice, after initial escape-oriented movements, develop an immobile posture when placed in an inescapable stressful situation. In this case, it involves the hemodynamic stress of being hung in an uncontrollable fashion by their tail (Cryan, Mombereau, & Vassout, 2005). One of the disadvantages of behavioral despair tests is that there is a weak analogy between the depression symptoms experienced by humans and the neurobiology that mediate the depressive-like behaviors in currently existing animal models.

A considerable number of studies used the repeated exogenous administration of glucocorticoids, at low doses, to mimic the dysfunction of the HPA axis in rodents (Sterner et al., 2010). This approach evokes significant changes in animal behavior and neurochemistry, including reduced neurogenesis, that parallel many of the core symptoms and neurobiological changes associated with human depression (Sterner et al., 2010). Recently some studies tried the single administration of dexamethasone as a trigger stimulus to evoke depressive-like behaviors in mice. This strategy induced changes in the mouse behavior assessed in the forced swimming test (Wróbel, Serefko, Wlaź, & Poleszak, 2014; Wróbel, Serefko, Wlaź, & Poleszak, 2015; Mesripour, Alhimma, & Hajhashemi, 2018). Aiming to add evidence to this acute neuroendocrine model of depression, this study sought to evaluate the behavioral effects of a single administration of dexamethasone in the tail suspension and splash tests in male and female mice. The effects of the classical antidepressants nortriptyline and venlafaxine were also tested in mice treated with a single dose of glucocorticoid. Our data showed that acute dexamethasone administration can be used as an animal model for depression because of: (a) feasibility, (b) predictive validity similar to the behavioral despair tests, and (c) ability to mimic the HPA axis dysfunction as observed in depressive patients.

Method

Animals

Experiments were performed using Swiss male and female mice bred at the Federal University of Rio Grande do Norte (Natal, Brazil). Mice were 12–14 weeks old (male: 38–44 g; female: 32–40 g) and were housed in plastic cages (33 × 40 × 17 cm) in groups of a maximum of 10 under standard conditions (22 ± 1°C; 12 h light:12 h dark cycle, lights on at 6:00 a.m.) with food and water ad libitum. A total number of 176 male and 176 female mice were used to develop this study; the number of animals per group was seven to eight, as detailed in the figure legends. For female mice, after a behavioral test, vaginal smears were collected, as described by Marcondes, Bianchi, and Tanno (2002). Smears were stained with a 2% methylene blue solution. According to the proportion of epithelial cells, cornified cells, and leukocytes, the estrous cycle phases were classified as proestrus, estrus, diestrus, and metaestrous. All behavioral tests were performed during the light cycle (between 10:00 a.m. and 1:00 p.m.). Behavioral studies were approved by the local Ethics Committee in the Use of Animals (Protocol No. 001/2016) and strictly followed the Brazilian Law No. 11.794/2008 for the care and use of experimental animals. This study is reported following the Animal Research Reporting In Vivo Experiments guidelines (Kilkenny et al., 2010).

Drugs and Treatments

Dexamethasone (0.07 mg/kg, subcutaneous [sc]; Sigma-Aldrich, St. Louis, MO) was solubilized in 10% ethanol and saline (0.9% NaCl), and it was stored at −20 °C (stoke solution: 0.1 mg/mL). A stored aliquot of dexamethasone was freshly solubilized before experiments in saline in a final concentration not exceeding 1.6% ethanol. The antidepressants nortriptyline (30 mg/kg, intraperitoneal [ip]; Novartis Biociências SA, São Paulo, Brazil) and venlafaxine (30 mg/kg, ip; Biosintética Farmacêutica Ltd., São Paulo, Brazil) were solubilized in saline. Negative controls were treated with the same concentration of solvents used to solubilize the drugs and by the same via of administration. All drugs injected were given in a volume of 10 mL/kg. The dosages of dexamethasone (Wróbel et al., 2014;

Wróbel et al., 2015), nortriptyline (Medeiros et al., 2015), and venlafaxine (Millan et al., 2001) used in this study were based on previous findings. A single administration of dexamethasone at similar dose evoked depressive-like effects in the forced swimming test (Wróbel et al., 2014; Wróbel et al., 2015), whereas conventional antidepressants reduced immobility time in the tail suspension test (Medeiros et al., 2015; Millan et al., 2001). Dexamethasone was administered 4 h, 24 h. or 7 days before behavioral evaluation, whereas acute nortriptyline (30 mg/kg) and venlafaxine (30 mg/kg) were administered 60 min prior to behavioral tests. Animals were randomly assigned for each experimental group. The observer was unaware of the treatment conditions.

Behavioral Tests

Tail suspension test. This behavioral assay was performed as previously described by our research group (Medeiros et al., 2015). Briefly, mice were isolated acoustically and visually and suspended 50 cm above the floor by an adhesive tape placed 1 cm from the tail tip. The test lasted 6 min and the total amount of time each animal remained immobile (i.e., did not struggle) during the session was registered (in seconds). Separate groups of animals were pretreated with dexamethasone 4 h, 24 h, or 7 days before behavioral evaluation in the tail suspension test. Additionally, to test the effects of conventional antidepressants in the dexamethasone-induced depressive-like behaviors, mice were pretreated with the glucocorticoid 4 h prior to the tail suspension test.

Open field test. Spontaneous locomotor activity of mice was assessed in the open field test. A squared black arena (40 × 40 × 40 cm) made of wood covered with impermeable formica was used. The behavioral assay was performed in a test room with dimly light condition. Each mouse was placed in the center of the open field and the distance traveled (in meters) during 5 min was registered. The arena was cleaned with 5% ethanol solution after behavioral evaluation of each mouse. This test was performed 30 min after the tail suspension test, and 4.30 h after the dexamethasone administration. All test sessions were recorded by video camera and analyzed with ANYmaze software, version 4.99 (Stoelting Co., Wood Dale, IL).

Splash test. This test consists of recording the latency to and the total amount of time that mice spent doing self-cleaning behaviors after squirting a sucrose solution (10%) on their dorsal coat. The sucrose solution viscosity instigates animals to self-lickingr. It is relevant to mention that impaired self-care is observed in depressive patients (American Psychiatric Association, 2013). This test was performed with some adjustments as previously reported (Yalcin, Aksu, & Belzung, 2005). Each animal was habituated to an oblong plastic cage (30 × 20 × 13 cm), with black floor and walls, for 20 min, and after this period, animals were squirted with sucrose solution. The test session lasted 6 min and the following parameters were manually registered: latency to the first grooming and total amount of time spent licking the coat (both registered in seconds). Cages were cleaned with 5% ethanol between sessions. This test was performed with mice exclusively subjected to this behavioral assay. Animals were pretreated with dexamethasone 4 h prior to this test.

Data Analysis

Data are presented as mean ± SEM of n animals. Data sets were initially checked for normality, with Shapiro-Wilk's test, before use of parametric statistical tests. Significant differences between two experimental groups were detected by using an independent Student's t test. Comparisons between the pretreatment with dexamethasone and the reversal effects of antidepressants were analyzed with two-way ANOVA followed by Bonferroni's post hoc test, with two independent factors: dexamethasone pretreatment and antidepressants administration. Differences were considered statistically significant when $p < .05$. Statistical analysis was performed using SPSS software, version 21.0 (IBM SPSS Statistics, OBS Software, São Paulo, Brazil) and GraphPad Prism, version 5.0 (Graph Pad Software Inc., San Diego, CA).

Results

Effects of Acute Dexamethasone Administration on Mouse Behavior

Male mice acutely treated with dexamethasone and exposed to the tail suspension Test 4 and 24 h after treatment displayed a significant increase in the immobility time when compared with its respective control group (Figure 1A, upper panel; Student's t test, $t[14] = 4.603$, $p < .001$; $t[14] = 3.093$, $p = .008$, respectively). However, male mice injected 7 days before the tail suspension test displayed a trend to reduce the immobility time when compared with controls (Figure 1A, upper panel; Student's t test, $t[14] = 1.905$, $p = .072$).

Accordingly, female mice acutely treated with dexamethasone 4 and 24 h before the tail suspension test also displayed a significant increase in the immobility time (Figure 1B, upper panel; Student's t test, $t[14] = 5.680$, $p < .001$; $t[14] = 2.641$, $p = .019$, respectively). However, no changes were observed in the tail suspension test 7 days after the single administration of dexamethasone in female mice (Figure 1B, upper panel; Student's t test, $t[14] = 0.682$, $p = .506$).

To investigate whether dexamethasone is able to affect locomotor activity, the total distance traveled was evaluated in the open field test in male and female mice. Dexamethasone did not induce any alteration in the spontaneous locomotion assessed in the open field test at 4 h, 24 h, and 7 days after treatment in both sexes (Figure 1, A and B, lower panel).

Effects of Conventional Antidepressants on Acute Dexamethasone-Induced Depressive-Like Behavior

The effects of nortriptyline, a tricyclic antidepressant, were evaluated at 4 h in dexamethasone-treated male and female mice in the tail suspension, open field, and splash tests. Considering male mice, an ANOVA revealed a significant interaction effect between the two independent factors: dexamethasone and nortriptyline (Figure 2A, upper panel; $F_{[1,28]} = 6.80$, $p = .014$). Post hoc analysis indicated a significant increase in the immobility time of mice treated with dexamethasone, which was blocked by nortriptyline. Similarly, a significant interaction effect between the independent factors dexamethasone and nortriptyline was also detected for female mice (Figure 2B, upper panel; $F_{[1,28]} = 10.08$, $p =$
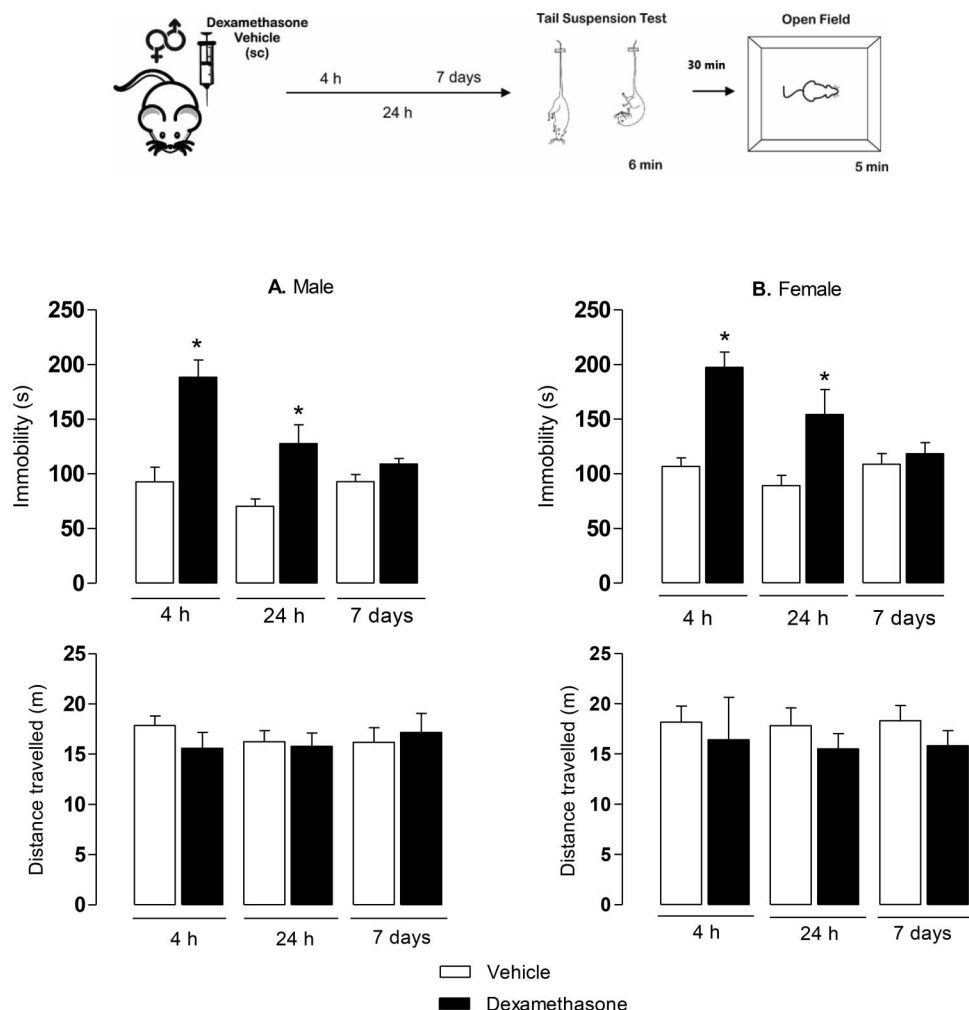
Figure 1. Effects of dexamethasone (0.07 mg/kg, sc) on immobility time in the tail suspension test and distance traveled in the open field test in male (A) and female (B) mice assessed 4 h, 24 h, and 7 days after administration (separate group of mice). Data are mean ± *SEM* of eight mice/group. * $p < .05$ versus vehicle, according to an unpaired Student's *t* test.

.004). Acute administration of dexamethasone increased immobility time in the tail suspension test, and the treatment with nortriptyline counteracted it.

As shown in the first set of experiments, the treatment with dexamethasone did not change the locomotor activity of male and female mice. However, nortriptyline affected distinctly mouse locomotion in male and female mice. In male mice, nortriptyline reduced the distance traveled in both control and dexamethasone-treated mice (Figure 2A, lower panel; two-way ANOVA, nortriptyline effect: $F_{[1,28]} = 17.73$, $p < .001$). However, the treatment with nortriptyline did not change spontaneous locomotion in control or dexamethasone-treated female mice (Figure 2B, lower panel; two-way ANOVA, $p > .05$).

The effects of the 5-hydroxytryptamine (5-HT) and noradrenaline reuptake inhibitor antidepressant venlafaxine were also assessed in dexamethasone-induced depressive-like behavior in male and female mice. According to a two-way ANOVA, an interaction effect between the two independent factors (i.e., dexamethasone and venlafaxine) was detected in the immobility time for male mice (Figure 3A, upper panel; $F_{[1,28]} = 14.26$, $p < .001$). Bonferroni's post hoc test revealed that venlafaxine blocked the dexamethasone-induced increase in the immobility time in the tail suspension test. In female mice, a two-way ANOVA indicated a significant effect for dexamethasone (Figure 3B, upper panel; $F_{[1,28]} = 18.30$, $p < .001$) and venlafaxine (Figure 3B, upper panel; $F_{[1,28]} = 51.24$, $p < .001$) factors, but an interaction effect between factors was not found ($F_{[1,28]} = 2.02$, $p = .166$). Bonferroni's post hoc analysis showed the treatment with venlafaxine reduced per se the immobility time compared to control and counteracted dexamethasone effects on immobility time in the tail suspension test.

As illustrated in Figure 3A (lower panel), venlafaxine reduced spontaneous locomotion in the open field test in male (two-way ANOVA, $F_{[1,28]} = 29.27$, $p < .001$) but not in female mice (Figure 3B, lower panel).

Figures 4 and 5 illustrate the effects of nortriptyline and venlafaxine on the behavior of male and female mice pretreated with a single dose of dexamethasone in the splash test.
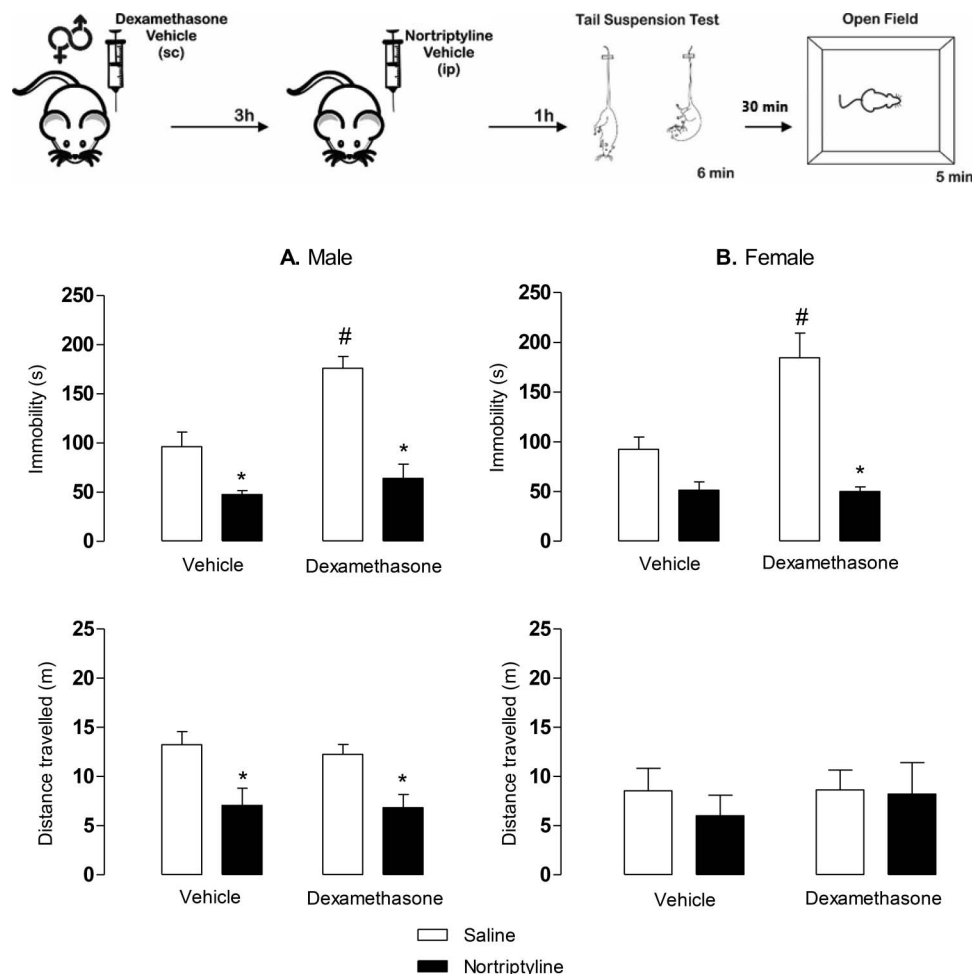
Figure 2. Effects of nortriptyline (30 mg/kg, ip) on immobility time and distance traveled in male (A) and female (B) acute dexamethasone (0.07 mg/kg, sc, 4 h prior to the test)–treated mice in the tail suspension and open field tests, respectively. Data are mean ± *SEM* of eight mice/group. * $p < .05$ versus its respective controls. # $p < .05$ versus vehicle. Two-way ANOVA, Bonferroni's test.

The treatment with dexamethasone increased the latency spent to the first self-grooming, but the acute administration of nortriptyline blocked it in male and female mice (Figure 4, A and B, upper panel; two-way ANOVA, interaction effect between dexamethasone and nortriptyline; male: $F_{[1,28]} = 5.28$, $p = .0293$; female: $F_{([1,26]} = 18.32$, $p = .0002$). Additionally, the administration of dexamethasone trended to reduce the time spent self-grooming in female mice, but it did not reach significance (Figure 4, A and B, lower panel; two-way ANOVA, dexamethasone effect; male: $F_{[1,28]} = 0.54$, $p > .05$; female: $F_{[1,26]} = 2.96$, $p = .0972$).

Concerning the effects of venlafaxine in the splash test, a two-way ANOVA revealed an interaction effect between the independent factors dexamethasone and antidepressant for the latency to self-care in male (Figure 4A, upper panel; $F_{[1,28]} = 14.57$, $p < .001$) and female (Figure 4B, upper panel; $F_{[1,28]} = 17.54$, $p < .001$) mice. Post hoc analysis indicated that dexamethasone increased the latency to the first self-grooming and the treatment with venlafaxine counteracted it. The total time spent self-licking was also registered. As shown in Figure 4 (lower panels), a

two-way ANOVA revealed an effect for the independent factor dexamethasone for both male and female mice ($F_{[1,28]} = 6.56$, $p = .016$; $F_{[1,28]} = 12.13$, $p = .002$, respectively).

The estrous cycle of the female mice was recorded after each experimental day. The percentage of mice at each estrous cycle phase was depicted in Supplemental Figures 1–4. Supplemental Figure 1 illustrates the percentage of animals at each estrous cycle phase in dexamethasone and vehicle group. A comparable number of mice at each estrous cycle phase was found for both groups. Thus, it excludes any confounding effect because of the prevalence of a given estrous cycle phase in vehicle and dexamethasone-treated groups. The same rationale can be applied for those experimental series in which the effects of nortriptyline and venlafaxine was assessed in the tail suspension and splash tests (Supplemental Figures 2–4).

Discussion

The present study adds new evidence to a neuroendocrine mouse model of depression induced by the acute administration of
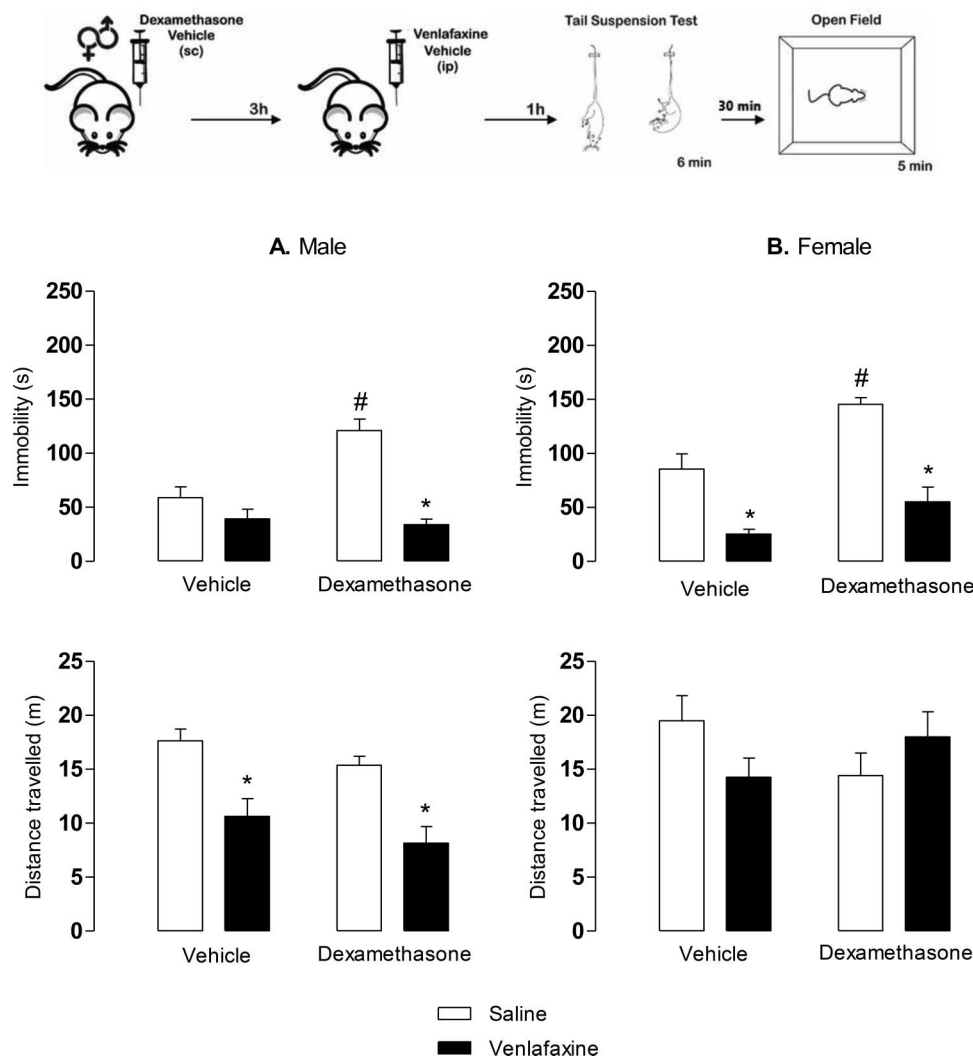
Figure 3. Effects of venlafaxine (30 mg/kg, ip) on the immobility time and distance traveled in male (A) and female (B) acute dexamethasone (0.07 mg/kg, sc, 4 h prior to the test)–treated mice in the tail suspension and open field tests, respectively. Data are the mean ± *SEM* of eight mice/group. * $p < .05$ versus its respective controls. # $p < .05$ versus vehicle. Two-way ANOVA, Bonferroni test.

dexamethasone in Swiss mice from both sexes. A single administration of a glucocorticoid drug evoked significant increase in the immobility time in the tail suspension test at 4 and 24 h but not 7 days after injection without affecting the spontaneous locomotion in the open field test. Our findings are consonant to previous studies that reported depressive-like behavior after acute administration of dexamethasone in mice (Mesripour et al., 2018; Wróbel et al., 2014, 2015).

Interestingly, it has been shown that acute exposure to corticosterone was unable to reduce the immobility time of rodents in behavioral despair tests (Johnson, Fournier, & Kalynchuk, 2006; Ago et al., 2008; Marks, Fournier, & Kalynchuk, 2009; Lussier, Romay-Tallón, Kalynchuk, & Caruncho, 2011). These differences are probably related to pharmacokinetic and pharmacodynamic distinctions between corticosterone and dexamethasone. In fact, dexamethasone is more potent, long lasting, and selective gluco-

corticoid receptor agonist compared with corticosterone (Czock, Keller, Rasche, & Häussler, 2005). In addition, a balance between mineralo (MR) and glucocorticoid receptors (GR) activation is proposed as a physiological response under a stressful event. Thus, an imbalance in MR:GR activation may induce HPA axis dysregulation, leading to impaired behavioral adaptation, which can enhance susceptibility to stress-related mental disorders (de Kloet, 2014). In this sense, dexamethasone evokes an imbalance of MR × GR activation, affecting brain functions in a distinct manner compared with the endogenous hormone corticosterone.

The findings described herein are relevant and may add evidence to a new animal model of depression. The main advantages of this acute neuroendocrine model of depression are: (a) a rapid depressogenic effect was induced by dexamethasone; (b) within the period of 24 h, more than one behavioral test using the same treated mouse can be conducted; (c) male and female mice (despite
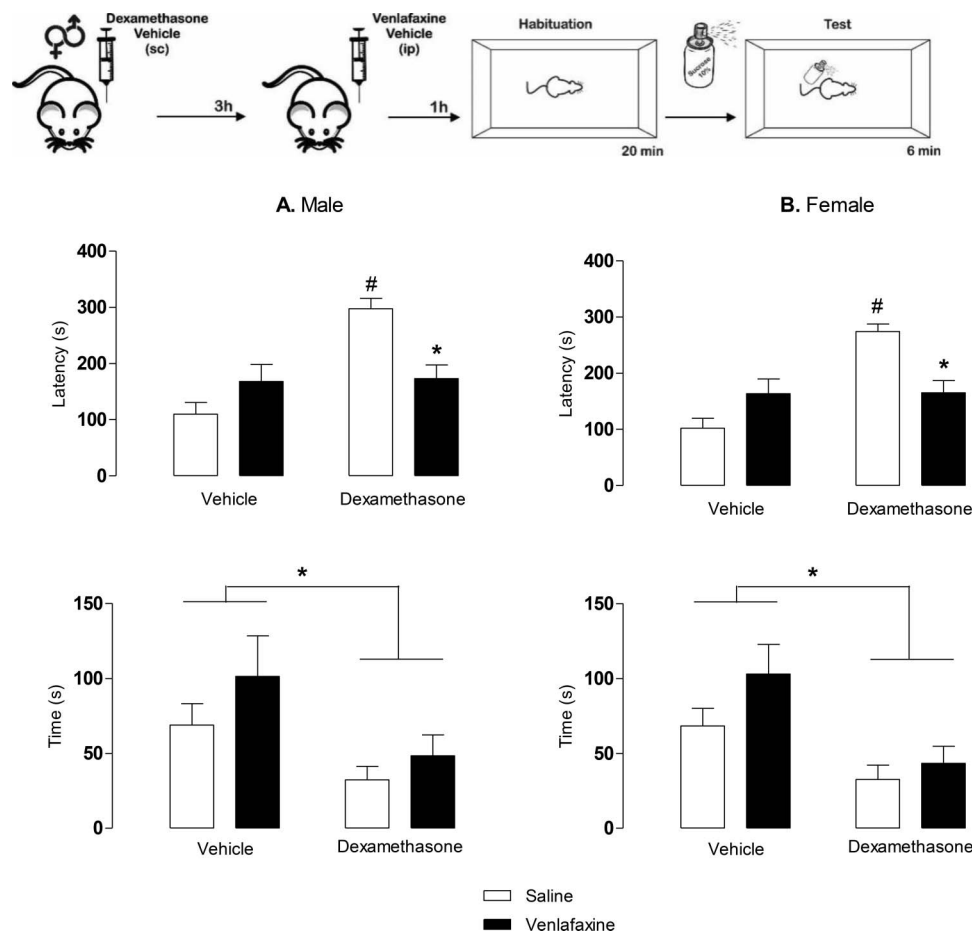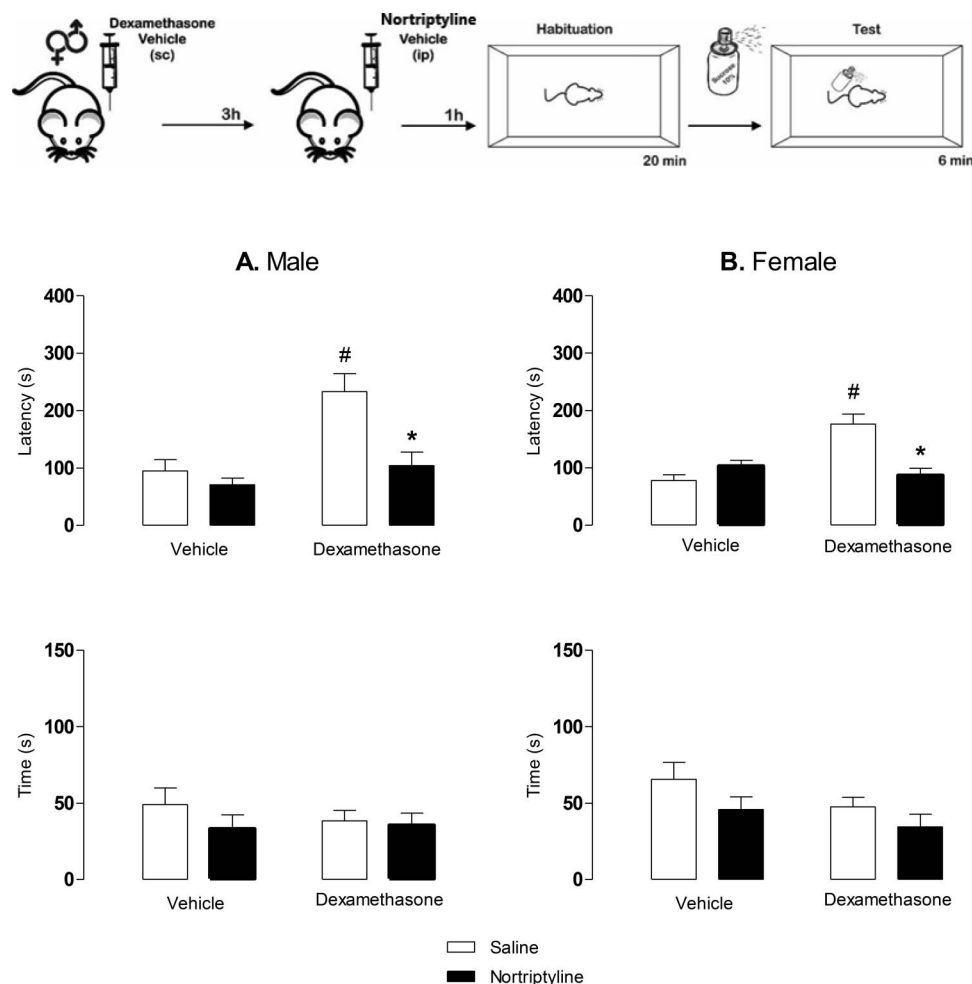
Figure 4. Effects of venlafaxine (30 mg/kg, ip) on the latency to the first self-grooming and the total time spent to self-care in the splash test in male (A) and female (B) acute dexamethasone (0.07 mg/kg, sc, 4 h prior to the test)–treated mice. Data are the mean $\pm$ *SEM* of eight mice/group. $^{*} p < .05$ versus saline. $^{\#} p < .05$ versus vehicle. Two-way ANOVA, Bonferroni test.

the estrous cycle phase) presented similar depressogenic behavior after acute dexamethasone administration; (d) increased the sensitivity of the tail suspension test to the effects of antidepressant drugs because as reported here a single administration of nortriptyline and venlafaxine, at doses widely showed to be antidepressant (for a review see: Cryan et al., 2005), did not consistently reduced immobility per se in the tail suspension test in male and female mice (Figures 2 and 3). Notably, test parameters and treatment-sensitive behavioral indices are not always the same for male and female rodents in animal models of depression, as reviewed by Kokras and Dalla (2014). Therefore, the animal model presented in this study is distinguished because mice from both sexes showed similar depressive-like behavior to acute dexamethasone administration, and then male and female mice can be easily compared using the same behavioral parameters.

The pharmacological validation of the dexamethasone-induced, depressive-like behaviors was also evaluated by testing the effects of two conventional antidepressants, nortriptyline and venlafaxine. Both drugs were able to counteract the glucocorticoid-induced depression in the tail suspension test. Accordingly, Wróbel et al. (2014) have showed that the antidepressants imipramine, amitrip-

tyline, tianeptine, mianserine, citalopram, and moclobemide were able to block the effects of a single dexamethasone administration in male mice in the forced swimming test. Altogether these data reinforce the view that antidepressants with distinct mechanisms of actions can minimize the depressogenic-like effects of acute dexamethasone administration. It is noteworthy to mention that nortriptyline and venlafaxine were able to reduce spontaneous locomotion in a sex-dependent manner, being male more affected than female mice. The mechanism related to this effect remains unknown calling for more research.

We also aimed to extend the face validity of this acute animal model of depression by investigating the effects of the single administration of dexamethasone in the splash test. This assay assesses motivational and self-care behaviors of rodents, which is generally reported to be affected by stressful situations (Czéh et al., 2016). In this study, we observed that 4 h after the administration of dexamethasone, mice consistently displayed an increase in the latency to self-licking. Moreover, acute administration of nortriptyline and velanfaxine significantly counteracted the latency to the first grooming in the splash test. It is known that chronic stressful situations (which induce depressive symptoms in rodents)

Figure 5. Effects of nortriptyline (30 mg/kg, ip) on the latency to the first self-grooming and the total time spent to self-care in the splash test in male (A) and female (B) acute dexamethasone (0.07 mg/kg, sc, 4 h prior to the test)–treated mice. Data are the mean $\pm$ *SEM* of seven to eight mice/group. * $p < .05$ versus saline. $^\#$ $p < .05$ versus vehicle. Two-way ANOVA, Bonferroni test.

suppress self-grooming in rodents (Ducottet, Aubert, & Belzung, 2004; Ducottet & Belzung, 2004; 2005). Additionally, rats showing longer spray-induced grooming under nonstressful conditions spend shorter immobility time in the forced swimming test (Shiota, Narikiyo, Masuda, & Aou, 2016), correlating the outcomes of the splash test to a depressive related behavior. As far as we know, this is first report of the impact of acute administration of dexamethasone on the mouse behavior assessed in the splash test and the effects of antidepressants in restoring dexamethasone-induced behavioral alterations in this test.

The neural mechanisms related to dexamethasone induced depressive-like behaviors are possibly based on the rapid neurochemical changes on monoamines in brain areas involved in the emotions. Previous studies have shown that rats acute treated with dexamethasone (a 10-fold higher dose as used in the present study, 0.7 mg/kg) presented a 5-HT-level decrease in the prefrontal cortex and hippocampus after 3 h of a single administration without altering dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, and 5-hydroxyindoleacetic acid levels in the prefrontal cortex, striatum,

amygdala, and hippocampus (Inoue & Koyama, 1996). Tsubota et al. (1999) also showed that higher doses of dexamethasone (2 mg/kg $\times$ two administrations) suppressed 5-HT turnover in the cerebral cortex and striatum, whereas dopamine turnover was enhanced in the striatum. Altogether these reports support the view that acute dexamethasone reduces monoamines, mainly 5-HT in the brain, which could contribute to the depressogenic effects observed after a single administration of this glucocorticoid. In this sense, acute administration of antidepressants, such as venlafaxine and nortriptyline, were able to block these altered behaviors by restoring the monoamines levels. Thus, other mechanisms have been proposed to elucidate the depressive actions of dexamethasone, particularly after long-term exposure to this drug. For instance, GR activation by dexamethasone impairs nerve growth factor–promoted neurite outgrowth and neuronal survival by interfering with the activation/phosphorylation of protein kinase B and extracellularly regulated kinase 1/2 (Terada et al., 2014). However, further studies are required to fully clarify whether these proposed pathways are also relevant to the acute effects of dexamethasone.

Conclusion

The present study adds new evidence to an acute neuroendocrine animal model of depression based on a single administration of dexamethasone in mice. In fact, glucocorticoid administration increased immobility in the tail suspension test and reduced self-care behavior in male and female mice. The administration of antidepressants venlafaxine and nortriptyline were able to block the depressogenic behaviors of dexamethasone in mice. These observations contribute to the development of a fast-inducing and feasible animal model of depression, which could be able to be performed in both sexes, displaying comparable face, construct, and predictive validity as the stress-induced animal models of depression.

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